ЖУРНАЛ ЭВОЛЮЦИОННОЙ БИОХИМИИ И ФИЗИОЛОГИИ, 2020, том 56, № 7, с. 732

МАТЕРИАЛЫ КОНФЕРЕНЦИИ И ШКОЛЫ

THE DEVELOPMENT OF STEROIDOGENIC FUNCTION REGULATORS BASED ON THIENOPYRIMIDINE DERIVATIVES, LUTEINIZING HORMONE RECEPTOR AGONISTS

© 2020 г. A. A. Bakhtyukov[1,*], K. V. Derkach[1], V. N. Sorokoumov[2], and A. O. Shpakov[1]

[1] *Sechenov Institute of Evolutionary Physiology and Biochemistry of the Russian Academy of Sciences, Saint Petersburg, Russia*

[2] *Institute of Chemistry, Saint Petersburg State University, Saint Petersburg, Russia*

**e-mail: bahtyukov@gmail.com*

DOI: 10.31857/S0044452920071468

The main regulator of steroidogenesis is luteinizing hormone (LH), which binds to and activates the ectodomain of the LH receptor (LHR). However, chronic administration of LH and its homolog, human chorionic gonadotropin (hCG), reduces the sensitivity of Leydig cells to gonadotropins, as a result of which the development of alternative activators of LHR is an urgent task. Of greatest interest are compounds based on thieno[2,3-*d*]pyrimidine structure, which bind to the allosteric site located in the transmembrane channel of the LHR. The aim of the work was to study the effect of the thieno[2,3-*d*]pyrimidines TP01, TP03, TP04, and TP21, which we first developed, on the basal activity of adenylyl cyclase (AC) in rat testicular membranes, on the level of testosterone (T) in the blood, the expression of steroidogenesis genes and the content of T in the testes of male rats with a single and three-day administration of thieno[2,3-*d*]pyrimidines. In the *in vitro* experiments, hCG increased the basal activity of AC in testicular membranes more efficiently than thieno[2,3-*d*]pyrimidines; and in the *in vivo* experiments in the case of a single administration, hCG (20–50 IU/rat) exceeded the most active compounds TP03 and TP04 (15–50 mg/kg) according to the steroidogenic effect. With a three-day administration, the hCG effect was weakened and was lower than the steroidogenic effects of TP03 and TP04. After a three-day hCG administration, in the testes, the expression of the *Star* and *Cyp11a1* genes encoding the transport StAR protein and cytochrome $P450_{scc}$ responsible for the synthesis of pregnenolone was increased, and the expression of the *Lhr* and *Cyp17a1* genes encoding the LHR and cytochrome P450-17α, responsible for the synthesis of androstenedione, was inhibited. Thieno[2,3-*d*]pyrimidines moderately stimulated the *Star* expression and did not affect the *Lhr* expression, indicating a mild stimulation of testicular steroidogenesis and the absence of an inhibitory effect on LHR expression, which allows the testes to remain sensitive to gonadotropins. These data indicate the potential of thieno[2,3-*d*]pyrimidines for controlled stimulation of steroidogenesis.

Supported by RSF 19-75-20122.